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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,060	02/08/2005	Zhiming Suo	US 1421/05 (VA)	4405

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DINESH AGARWAL, P.C.
5350 SHAWNEE ROAD
SUITE 330
ALEXANDRIA, VA 22312

EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/524,060	SUO ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-34* is/are pending in the application.

4a) Of the above claim(s) *3,5,6,8 and 14-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,9-13 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

Applicant's amendment filed May 11, 2006 is acknowledged. Claim 4 is cancelled. Claims 1-3, 5-33 and newly added claim 34 are pending in this application. Claims 3, 5, 6, 8, 14-33 are withdrawn. Claims 1, 2, 7, 9-13 and new claim 34 are under examination in light of a method of detecting early stages of Alzheimer's pathogenesis in vitro or in a transgenic model comprising detecting a disruption in normal distribution of a G-protein receptor kinase (GRK5). The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to claim 4 as encompassing non-elected subject matter is withdrawn in response to Applicant's amendment canceling the claim.

The rejection of claim 4 under 35 U.S.C. 112, first paragraph, as lacking enablement commensurate in scope with the claims is withdrawn in response to Applicant's cancellation of this claim.

Claim Rejections/Objections maintained

The rejection of Claims 1, 2, 7, and 9-13 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a disruption in normal cellular distribution of a G-protein receptor kinase 2/5 (GRK2/5) in association with a

transgenic model with early onset of Alzheimer's disease (AD), CRND8 mice, does not reasonably provide enablement for disruption of all forms of GRK distribution and also for detecting all the Alzheimer's pathogenesis as broadly claimed is maintained for reasons of record in the previous office action. In addition, the rejection of these claims because, while being enabling for detecting the disruption in normal distribution of GRK2/5, the specification does not reasonably provide enablement for detecting the pathogenesis of AD by using soluble β-amyloid peptides in a diagnostic method is maintained. The rejection is also applied to newly added claim 34.

Applicant argues that claim 1 has been amended to recite in vitro and a transgenic model as well as early stage, which are fully supported and enabled by the instant specification. Applicant also argues that the disruption of GRK2/5 distribution results in prolonged GPCR signaling and potentiating inflammatory responses via GPCR, which is supported by the specification. Applicant's arguments have been fully considered but they are not persuasive. Applicant discloses that the distribution of GRK5 in cultured microglial cells in vitro changes after stimulating with soluble Ab1-42/1-40. Although Applicant discloses that the change of the cellular distribution of GRK5 after stimulating with soluble Aβ1-42/1-40 peptide can be detected by immunocytochemistry using anti-GRK5 antibody in vitro, Applicant fails to provide enough guidance as to how to detect a distribution of GRK5 in vivo and also by a peptide as recited in the claim 34. Applicant fails to demonstrate that what specific structures/characteristics are required for a peptide to detect the distribution of GRK5 since the distribution of GRK5 is not only on the membrane-bound location but also in

the cytosol; there is no information showing that any peptide or even soluble Aβ peptide binds to GRK5 directly. In addition, Applicant fails to demonstrate the current method can be used to detect the pathogenesis in vivo. There is no guidance to enablement one of skill in the art to administering soluble Ab peptide to a live subject to detect the change of cellular distribution of GRK5 in vivo and further conclude the change of cellular distribution of GRK5 is the cause of AD at the early stage. Further, although Applicant discloses that there is less GRK5 in the membrane fraction than cytosolic fraction in brain extracts derived from postmortem AD patients and TgCRND8 mice as detected by SDS-PAGE/Western blot, Applicant fails to provide guidance as to how this finding can be used to detect the pathogenesis of AD at early stage or prodromal stage. Since the symptoms of AD are progressively worse and dependent on age, the detection of less GRK5 in the membrane fraction in these test samples does not conclude that the change of cellular distribution of GRK5 is the pathogenesis of AD at early stages. In addition, the samples are derived from patients who die of AD; thus there is no way to find out whether the change of GRK5 is an indicator for prodromal stage of AD. Moreover, since AD is a multifactor pathogenesis disease, whether detecting the change of the cellular distribution of GRK5 can detect early stage Alzheimer's pathogenesis is unpredictable, indicating undue experimentation is required. Accordingly, the rejection of claims 1, 2, 7, 9-13 and 34 under 35 U.S.C. §112, first paragraph, as the specification would not be enabling for disrupting all forms of GRK distribution and detecting all the Alzheimer's pathogens by using soluble β-amyloid peptides in a diagnostic method is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Claims are drawn to a method of detecting early stages of Alzheimer's pathogenesis in vitro or in a transgenic model and a method of detecting a disruption in normal cellular distribution of G-protein receptor kinase 5 (GRK5) by using a peptide. Applicant fails to provide enough guidance as to what particular structure is required for a peptide can be used to detect the disruption of normal distribution of GRK5 recited in the claim 7 and 34. Applicant is in possession of β-amyloid peptide 1-42/1-40 which can be used to stimulate the

change of GRK5 distribution. However, Applicant is not in possession of other soluble peptides that can disrupt the normal distribution of GRK5 other than β-amyloid peptide 1-42. Applicant only discloses a limited number of species of soluble β-amyloid peptide; therefore, the skilled artisan cannot envision all contemplated possibilities of peptides. The specification fails to define the particular conserved structures/characteristics for a peptide that is required for disrupting cellular distribution of GRK5 as recited in the claims 7 and 34. The skilled artisan cannot envision all contemplated possibilities recited in the instant claims. Since the structure/characteristics of the peptide are not unknown, a skilled artisan cannot contemplate the functional correlations of the effects with the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics for a peptide that is able to detect the disruption of the normal distribution of GRK5, the specification does not provide adequate written description of the claimed genus of peptide. Adequate written description requires more than a mere statement that it is part of the invention. A description of a genus of polypeptides/ compounds may be achieved by means of a recitation of a representative number of polypeptide sequences/chemical groups, defined by amino acid sequence/chemical structure, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the

invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398. The skilled artisan cannot envision the detailed chemical structure of the encompassed intracellular structure component, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, a method of detecting early stages of Alzheimer's pathogenesis in vitro or in a transgenic model and a method of detecting a disruption in normal cellular distribution of G-protein receptor kinase 5 (GRK5) by using a peptide have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 7, 9-13, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to detect and evaluate the cellular disruption in cells as recited in the claims 1 and 34 and further to draw a conclusion that the disrupted cellular distribution of GRK5 in brain cells is a cause of early stages of Alzheimer's disease as recited in the claim 1.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
July 5, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER